Differences in the interpretation of the GLP requirements by OECD monitoring authorities: the point of view from the pharmaceutical industry

Raymond K. Lowing

GLP Quality & Compliance, Sanofi-Aventis Research & Development, Chilly-Mazarin, France

Summary. The need to harmonise the principles of good laboratory practice (GLP), their application and their monitoring has always been a preoccupation of the authorities. This can be seen by the very early publication of the set of Organisation for Economic Co-operation and Development (OECD) documents, the training of the national inspectors, and the system of joint mutual visits. These aspects are now, for the most part, aligned. However, often the expectations of the inspectors and the interpretation behind the text are different and sometimes even opposite. In Sanofi-Aventis there is an almost unique position having 12 research and development sites in 7 different countries, all performing phases of studies which can be used by any of the other sites and all inspected by monitoring authorities (MAs) of the OECD GLP system. As with most international pharmaceutical companies a large majority of studies are multisite and even multicountry. This paper illustrates some of the challenges which are encountered when a global system of high quality is established to satisfy all the expectations of the multiple MAs, with particular reference to the diversity of origins of the requirements, specific guidance documents on GLP, question and answer sessions on GLP interpretations, annex requirements on specific areas (21 CFR Part 11, veterinary legislation etc.) and conference presentations by MAs. It is important to realize that even though there might be interpretations that the industry has some difficulty in understanding, the objective of this paper is not to complain or to criticize one or other of the MAs. Rather, the objective is to try to be constructive and to show where there are differences so that industry and the MAs can work together to establish systems which possess the level of quality necessary to ensure the safety of patients and the marketing of efficient products.

Key words: good laboratory practice, pharmaceutical industry, compliance with regulations.

Riassunto *(Diversità nell' interpretazione dei requisiti di BPL da parte delle autorità di monitoraggio dell'OCSE: il punto di vista dell'industria farmaceutica).* La necessità di armonizzare i principi di buona pratica di laboratorio (BPL) e la loro applicazione e verifica è sempre stata una preoccupazione delle autorità. La tempestiva pubblicazione di documenti dell'Organizzazione per la Cooperazione e lo Sviluppo Economico (OCSE) su tale materia, l'addestramento degli ispettori nazionali ed il sistema di visite congiunte reciproche sono una chiara dimostrazione di tale impegno. Questi aspetti sono oggi in larga misura allineati. Spesso, d'altra parte, le attese degli ispettori e l'interpretazione dei testi dei provvedimenti vigenti non collimano e sono talvolta addirittura in conflitto. La Sanofi-Aventis ha adottato una posizione pressoché univoca dal momento che essa consiste di 12 centri di ricerca e sviluppo in 7 paesi diversi, tutti impegnati in fasi di studi che possono essere usate da uno qualunque degli altri siti, tutti ispezionabili dalle autorità di monitoraggio (AM) aderenti al programma per la BPL dell'OCSE. Come avviene per la maggior parte delle aziende farmaceutiche internazionali, gli studi effettuati sono per lo più multisito, se non anche multinazionali. Questo articolo illustra alcune delle sfide da affrontare quando un sistema globale di alta qualità viene costituito per soddisfare tutte le attese di più AM, con particolare riferimento alla diversità delle cause delle richieste, a specifici documenti guida sulla BPL, alle sessioni di domande e risposte sull' interpretazione dei principi di BPL, ai requisiti derivanti da settori specifici (la sezione 11 del CFR 21, la legislazione veterinaria ecc.,) ed alle comunicazioni congressuali fatte dalle AM. È importante rendersi conto che anche se possono esserci interpretazioni che l'industria ha difficoltà a comprendere, lo scopo di questo articolo non è formulare critiche o lamentele sull'operato di una o più AM, ma piuttosto quello di cercare di essere costruttivi e di mostrare dove siano le diversità in modo tale che l'industria e le AM possano lavorare insieme per mettere a punto sistemi che posseggano il livello di qualità necessario per garantire la sicurezza del paziente e la commercializzazione di prodotti efficaci.

Parole chiave: buona pratica di laboratorio, industria farmaceutica, conformità ai regolamenti.

Address for correspondence: R. K. Lowing, GLP Quality & Compliance, Sanofi-Aventis Research & Development, 1 Avenue Pierre Brossolette 91385 Chilly-Mazarin, France. E-mail: raymond.lowing@sanofi-aventis.com.

INTRODUCTION

More than 80% of the studies performed by Sanofi-Aventis are multi-site non-clinical safety studies. All the 12 sites participating in such studies, therefore, cross international and inter-continental borders. The studies are all used in submission dossiers in all regions, *e.g.*, Japan, USA, Europe, and the rest of the world and these sites have received so far around 18 good laboratory practice (GLP) inspections from national GLP monitoring authorities (MAs) from the 7 countries in the last two years, thus providing a large amount of information concerning the different expectations of the various national authorities.

From a quality point of view, the best way to ensure high quality level of the activities is to have consistency in the way operations are performed. This implies the use of harmonised processes in a site for all studies no matter with which other site or country the study is being performed. A harmonised global quality system is therefore the optimum way of working. The challenge is therefore to establish a global system ensuring that all sites are capable of satisfying global standards and inspections from any MA as well as in a number of cases satisfying specific local requirements without overcomplicating the processes and increasing risks. This challenge would be much easier if there is consensus between the MAs in their interpretations of the requirements needed to comply with the principles of GLP. In the following sections some areas are shown where such a consensus is not present or where there are questions which remain to be answered.

MAJOR CHALLENGES

Where to obtain information on inspector's expectations

In the past, industry quality assurance (QA) staff were able to know what the inspectors expectations and interpretations were by making themselves aware only of the GLP legislation in their country. Now however, it is not so simple since requirements are coming from many different places, including: *i)* OECD principles of GLP and consensus documents; *ii)* FDA, European, Japanese or other National GLPs; *iii)* national Guidelines; *iv)* national question and answer sessions; *v)* conference presentations; *vi)* inspection outcomes.

The OECD very early on identified the need to prevent, or at least, limit multiple series of GLP requirements and this was the basis of the OECD guideline preparation process in the early 1980's and the expected cascading down to the participating countries of the OECD principles of GLP into local legislations, this process being backed up by OECD guidance and consensus documents, cross-training of the inspectors from the different countries, the OECD expert groups and the system of joint visits [1]. The cascading down of the same text concerning the principles has worked well. There remains the fact that the FDA legislation and the Japanese legislations have not implemented the OECD text [2, 3]. However, work on updating the text is ongoing in these two countries.

Even in countries where the text is the same there are still some MAs with specific requirements and who have also incorporated more or less subtle modifications to the text which mean that specific country requirements documented in the legislations are still present which must be known and taken into account when trying to establish a global quality system. Apart from these textual differences, variations in the expectations of the MAs are seen in a number of other areas which are less known, but which are still as important. Some examples are highlighted in the following sections.

National question and answer sessions

These sessions can be of several types and are interesting since they often give the details of the expectations of the MAs. Japan, for example, has a formal documented set of questions and answers which are regularly published and to which the industry is expected to adhere [4]. At the time of the initial FDA GLP implementation there were a number of question and answer sessions which were well documented. Such official FDA positions are now less frequent. However, there are question and answer sessions at many conferences in which MAs participate where questions are asked directly to the inspectors. Answers may be given and sometimes documented in the minutes of the conferences. Such unofficial replies are always pre-ceded by the caveat that the replies are personal opinions and do not necessarily represent the view of the agency. They are however important to know. If such opinions are made in QA conferences, then those in the QA arena are aware of them. On the other hand, the regulatory authority (RA) representatives are present in many other forums organised by other industry groups and during which there are either question and answer sessions or, more importantly, working groups which produce position papers or even publications. It is not so easy for QA staff to participate in such groups or even know of the outcome of such meetings.

Joint industry regulatory authority meetings resulting in new expectations

Some examples in this context are as follows: *i)* the joint industry, FDA, and suppliers working group organised by the DIA on the use of computerised systems in the GLP area. This was the so-called Red Apple Conference, which initially published a detailed book on the subject in 1987 and a second version in 2008 following meetings of the group during 2006 and 2007 [5]. Since FDA experts participated actively in this group it can generally be accepted that the publication identifies their expectations with respect to GLP compliance requirement during the life cycle of computer systems. This document, however, is practically unknown: *ii)* the joint US pharmacokinetic group meeting with the FDA in

Crystal City near Washington. A number of specific expectations were given by the FDA containing run Quality Control (QC) sample positions, numbers and acceptance criteria as well as a need to re-analyse real samples to ensure method ruggedness. The Crystal City meeting resulted in a white paper [6]. This document identifies expectations from an MA which is not legislation nor even an official document. However industry is expected to comply with these new expectations during GLP inspections even though there is no GLP text covering these aspects.

Freedom of information of inspection results following GLP inspections

In some countries it is possible to go to the MA website and find information on inspection findings. These are fairly useful, but sometimes, for obvious confidentiality reasons, there is insufficient data to be able to completely or correctly interpret the information. The FDA 483 information is well known and useful for this type of information. However, such systems are also available in other countries, but this is not generally known to the industry of that country.

DIFFERENCES IN INTERPRETATION AND EXPECTATIONS BETWEEN GLP MAs

Definition of multi-site studies

The OECD definition of multi-site studies as documented in the OECD Consensus Document 13 is "any study that has phases conducted at more than one site. Multi-site studies become necessary if there is a need to use sites that are geographically remote, organisationally distinct or otherwise separated." [7]. Although this definition appears clear, it has resulted in many different interpretations in what is a multi-site study. One other obvious challenge is the quite often cited FDA regulations which were not modified to take into account the OECD principles of GLP as was the case in all other countries. This occasionally causes difficulties with respect to the roles and responsibilities when USA sites are working with sites outside of the USA. A second example is the case where, rather than perform a multi-site study, companies, with the agreement of the MAs, take the phase to be performed at a separate site out of the study and perform a separate study, even if the link between the phase and the study is irrefutable. Such a process, although accepted by some countries, would be completely forbidden by others where the dictum of one protocol - one study - one study report is an absolute requirement. Working between two countries with such diametrically opposed interpretations is difficult.

In other countries there is a very flexible interpretation of what is geographically or organisationally distinct. In one country the MA has agreed that in a situation where two sites of the same company which are about 150 km apart and are performing different phases of the same study can do this as a mono-site study. However, in other cases/countries this may well be required to be performed as a multi-site study due to the fact that the study director (SD) could not personally and easily oversee the activities at the two sites.

Definition of test facility management

The OECD principles of GLP state that test facility (TF) management "means the person(s) who has the authority and formal responsibility for the organisation and functioning of the test facility according to these principles of GLP". It is important to note the plural form of the word "person(s)", indicating that this can mean an identified team of people. However, the confirmed Japanese interpretation insists that TF management must be one single person. This means for them that this person signs all study plans, all standard operating procedures (SOPS), receives all QA audit reports, *etc.* Such an interpretation is very strict and certainly makes it difficult to organise a global quality system.

Roles and responsibilities of study directors and principal investigators

It is clearly defined that the SD has the overall responsibility of the study, but what responsibility the principal investigator (PI) really has is less clear. Among different authorities the PI responsibility varies between two completely divergent attitudes: *i)* the PI must be able to show independence and particularly there be no influence from the SD during the preparation of the phase report; *ii)* the PI is a letter box and cannot make any technical or scientific decisions without prior agreement of the SD. As is clearly obvious, such opposing requirements from different MAs cannot coexist. During one inspection the MA spent a long time reading e-mails between the SD and PI to ensure that modifications to a draft report were not forced on a PI, whereas in another country the inspectors spent a long time trying to ensure that there was close discussion between the two actors. How can one differentiate between pressure and discussion when trying to satisfy all authorities and establish a global system is still open to debate. As well as the content of the phase reports, similar questions also often arise concerning who has the responsibility of deciding the impact of technical deviations occurring during the experimental part of the phase.

Phase plans in multi-site studies

The OECD principles of GLP require that there be one single study plan and that this be submitted to the PI who ensures that the information is correct. There is no mention of a "phase plan" being required to be produced either in the OECD principles or in the OECD Consensus Document 13 [7]. However, several MAs are expecting such phase plans to be produced, signed by the PI, and sent to the SD. In some countries the expectations go even further, identifying specific information to be included. Such information can include detailed run sequences and analyti-

cal methods. Some MAs also require that the phase plan be signed prior to the signature of the formal study plan by the SD and incorporated as an annex to the study plan. If there are any changes, *e.g.*, clotted samples not needed to be analysed, then an MA also requires that this be subject to an amendment to the phase plan and sent to the SD for inclusion in the formal study plan. For a phase concerning the statistical analysis of pharmacokinetic data, an MA has also requested that an amendment to the phase plan be made to include the actual bio-analytical results which are to be analysed statistically.

Certainly the SD must identify, in the study plan, sufficient information such that the PI knows what the phase concerns and gives sufficient information that they receive the correct information and specimens in the correct conditions. Also the SD should be globally aware of how the phase will be conducted and that the methods have been validated. However, to move from these general expectations to that of having a supplementary formal document, currently not required in any GLP principles and identifying specific requirements as to the type of information it should include, seems to be unnecessary and is already producing divergences among different MAs. The current situation is that some MAs require such satellite plans, some MAs are neutral, others have however, indicated that they do not want to see such satellite phase plans. With such a diversity of opinions it is impossible in a global environment to satisfy all the MAs who may be involved in inspecting phases of GLP studies.

Phase reports in multi-site studies

The OECD principles of GLP state that the reports from the PIs should be signed by them. However, in the OECD Consensus Document 13 on the conduct of multi-site studies it is required that the PI "supplies the SD with contributions which enable the preparation of the final report [7]. These contributions should include written assurance from the PI confirming the GLP compliance of the work for which he/she is responsible". The principles also give the option of preparing a phase report by saying that "It might be useful for the PIs to produce a signed and dated report". This shows that a phase report is not an obligation. However, among the MAs of the various countries there are differences in the requirements, with some going so far as to criticise the content of a phase report which, one should remember, is not an official document. There are in fact ever increasing requirements for the content of such documents among MAs in countries applying the OECD principles of GLP more and more details concerning methods even where SOPs are present, positioning of QC samples in analytical runs *etc.*

Contributing scientist reports

There are major differences between the FDA legislation and the national regulations in European countries when applying the OECD principles of GLP. This concerns the FDA requirement that *individual scientists* must produce signed contributions and that these must be included in the final study report. This FDA requirement also applies when the scientists are on the same site as the SD and continues to provoke a lot of discussion between industry and the FDA since it goes well beyond the OECD requirements. For studies which are going to be included in global submissions it renders the OECD principles of GLP inappropriate since FDA will expect this requirement to be met, as witnessed by FDA inspections of studies performed in Europe. It is difficult to understand such specific requirements concerning studies performed according to a National European GLP Legislation since, according to the OECD agreements, compliance to European GLP legislation is acceptable to the FDA. Another difficulty in following this specific FDA requirement lies in knowing for which *individual scientists* such signed reports are required. It is certain that without signed reports from the pathologists a major criticism from the FDA in the form of an FDA 483 will be forthcoming. However, it is extremely difficult to obtain information on which other scientists are concerned. Does this include ophthalmologists for eye examination results, cardiologists for electrocardiogram interpretations, clinical biochemists for haematology or clinical chemistry results? Where does the requirement stop?

Internal metrology

During the last couple of years inspectors are becoming more and more interested in the aspects of equipment qualification, maintenance, calibration and daily checks. Such interest occasionally results in apparent expectations which are difficult to understand by industry. The OECD principles of GLP require that "apparatus in a study should be periodically inspected, maintained and calibrated. Calibration should, where appropriate, be linked to national or international standards of measure". Certain MAs are taking this to mean that not only should the official calibration of the equipment be linked to the national standards, but also that each laboratory should perform its daily fit-for-use checks against using the officially registered standards, neither standard weights nor the internal standards of many such systems being acceptable. For example, in a laboratory where weighing balances are present in a number of different laboratories, the MA expected that a set of standard calibrants, linked to the National Standard, be present in each laboratory. Critical observations have also been given by MAs in situations where, following routine use, the automatic hand pipettes are stored horizontally and not vertically, even though there is no requirement or guidance on this from the instrument supplier.

External metrology

In situations where the equipment is sent to a supplier for maintenance or recalibration, certain MAs are expecting that: *i)* QA goes to audit the company

performing the maintenance; *ii)* QA audits the contract with the company performing the maintenance; *iii)* the laboratory endorses the SOPs used by the company to perform the metrology. None of these expectations concerning internal or external metrology seem to be included in the GLP principles and the benefit of such expectations to the level of quality of the studies performed is difficult to ascertain and explain to the operational departments.

Electronic raw data and electronic archiving

Many companies are moving towards, or are already heavily involved in, the use on real-time on-line acquisition of data. One of the most important areas of this aspect is the definition of the raw data and of the method of electronic archiving. Many international companies using such global systems for on-line data capture of, *e.g.*, pharmacokinetic data, are trying to develop systems which cross country borders using a common centralized archiving process. Experience has however shown that not all MAs have the same interpretation of what can be identified as raw data and what needs to be archived even for the same computer system, some MAs countries are saying that all should be electronic, whereas, for the same system, other MAs are requiring some parts of the information to be printed out and archived as signed paper copies. This leads to confusion and major challenges when such different requirements are seen with global computerised systems.

Support for electronic archive back-ups

During one inspection a computerised system was explained to an inspector with the electronic archiving process on a computer network with a separate back-up. The inspector however, still wanted all the data to have a second back-up, this time on CDs. Given the well known deficiencies and durability problems of CDs when compared to archiving on the network, it is difficult to convince operational staff of the pertinence of this GLP requirement which, as well as decreasing the respect that the operational staff have for the GLPs, makes it difficult to establish a comprehensible global archiving system.

Outstanding question on format of archived electronic data

Although there is little inspection activity on the following point it will be necessary in the near future to have some feedback from MAs with respect to the format of the archived information, particularly concerning how long archiving of data should be performed using the native, original format of the data capture, before being allowed to transform the data to a perennial re-readable, but untreatable format.

Global validation for global computerized systems

When one talks about computerised systems being used at several sites the issues about cross site or centralised validation occurs. Different MAs seem to have different opinions about:

1. what can be done once, but for which the results of the tests can be applicable to all sites;
2. which documentation must be permanently present on all sites;
3. of that which is central, what should be available to demonstrate that the secondary sites were aware of the validation results and agreed to its being used;
4. in how much time and in what format should the information be made available to the MAs for inspection.

Master schedule

The OECD definition of a master schedule is relatively simple being "a compilation of information to assist in the assessment of workload and for the tracking of studies at a test facility". This definition moved away from the original definition which implied the production of a table, due to the realisation during the 1997 update of the OECD principles of GLP that many pharmaceutical companies are now using computerized systems for planning and that many of such systems are global and cover all departments. However, during inspections there are still requests from certain MAs for tables with specific information (sometimes differing among MAs). For example, some authorities request that the date or archiving be included in the master schedule even though this information was not even requested in the initial GLP principles. There are still some difficulties in MAs accepting that: *i)* a master schedule be electronic rather than a paper table format; *ii)* that the information be under the responsibility of someone else than QA; *iii)* that more than GLP studies/activities be included on the master schedule. There are equally many country specific requirements concerning the exact content of the master schedule, the frequency of the printout of paper copies, and the frequency of the "archiving" of the information. Due to the national differences, it is not possible to set up a global system that can satisfy all MAs and local site systems are having to be set up with the obvious disadvantages when the planning of multi-site studies concerning several countries need to be integrated.

Quality assurance programme and responsibilities

There are well known differences in the regulatory texts concerning the audit requirements of the QA programmes between the FDA and the OECD countries. The major differences are the FDA requirement that practical phases of all studies be audited, whereas the OECD does not require that all studies be audited, but permits the use of process audits under certain conditions. It is obvious therefore, that a global system of QA audits must take this difference into account. There are however a number of other specificities in certain countries which are also a challenge. For example, Japan PMDA requires that a specific auditor be assigned to each study. They have also required that the fi-

nal study report be audited after the signature of the report by the SD. This obviously means that any corrections to the final report required following the QA audit would need to be done by amendment and the QA statement required to be included in the final study report could not be included in the report, but would need to be appended to it. Apparently these latter requirements may be in the process of being re-examined by the PMDA, although, at the time of preparing this article no documentation on this change in expectation is currently available.

Other MAs also have specific requirements which may not seem to be extremely important, but which make use of a global computerised system for the management of QA audits preparation, distribution of audit reports and the electronic replies to these reports impossible to implement across all sites. The first of such requirements concerns an MA which requires that there be a signature by the TF/Test Site (TS) management to confirm that they have read the QA audit report. This signature is required even when the computerised system has the electronically signed replies of the SD and the system can prove that the electronic report had been sent to the management together with the date and time of distribution of the report. It must be remembered that the GLP principles only require that the dates of distribution of the audit reports be maintained.

Other requirements, though not by the same MA, include the need for the QA of a TF to send a signed document to the QA of the TS to confirm that the TF QA is in agreement with the content of the study plan. Note that this concerns the content and not the GLP compliance of the study plan and therefore can be interpreted as including the scientific aspects of the plan.

Test item

Some major differences occur with respect to the expectations of the MAs concerning the analysis of the bulk test article. These differences are so marked that in some companies it would involve R&D re-organisation if complete GLP compliance is required in all countries. Europe accepts that the bulk test article used for animal testing can be analysed using the high analytical standards required by Good manufacturing practice (GMP) which ensure patient safety with no need to include in the SD compliance statement that this aspect was not performed according to the GLP principles. However, for both the FDA and Japan it is required that the same analysis must be performed according to the GLP principles. Otherwise, they expect a GLP non-compliance statement for this aspect of the study to be included in the final study report. On many occasions this point has been re-confirmed by representatives of the MAs concerned.

Complementary information required to a finalized study report

On a number of occasions, mainly following requests from RA reviewers, supplementary information is required to be supplied. This can include, *e.g.*, supplementary slides being prepared and read to confirm pathology diagnosis or supplementary statistical analysis. There are two completely opposite expectations from MAs on how to add this new GLP work to a given study once the report has been finalized. These differences make it impossible to satisfy everyone on this subject. The first, and most frequently accepted, option is to amend the initial study plan to indicate the new work and to create an amendment to the final study report to include the new information. One major MA, however, does not accept this process. They require that, for any new, supplementary work on a study for which the final study report has been signed, a new study is started with a completely different study plan and a new final study report. It is difficult to see how in the second option consolidated statistical analyses can be performed between the series of results obtained in the first report and those obtained in the second study required for the supplementary studies. One thing is however certain: it is impossible to satisfy completely opposite regulatory expectations.

Premature termination of a study due to the development of the compound being stopped (terminated study reports)

Once again, there are major differences between the expectations of the MAs in such situations. Such differences concern the type of reports which need to be produced, the involvement of the QA staff and the GLP status of such studies. A number of MAs do not consider it unusual, following suitable study plan amendments with adequate explanations, that the study be stopped and that the laboratory does not waste time on any unnecessary work either by the operational staff or by the QA staff. Since not all aspects of the initial plan were completed, then the study can be downgraded to non-GLP compliant. FDA, however, has the completely opposite point of view in that firstly the study cannot have its GLP status downgraded. It must remain as a GLP compliant study. A study report of some kind must be prepared and the QA personnel must review the report. Other MAs have a third option where they have no objection to the study being downgraded, but a report must be produced which includes a summary of the results obtained. It is difficult to understand these differences among the expectations. Although many pharmaceutical companies are willing to ensure the complete archiving and the documentation of this in a very short "terminated study report" such that everything can be recuperated with the exact indication of the study status at the time of termination, it is difficult for them to understand the extra requirements and workload. This is particularly true since the MAs have also indicated that their requirements do not differ between compounds for which the development has been stopped before going into clinical trials or after human exposure.

Bio-analysis clinical and pre-clinical pharmacokinetics

When this subject is discussed there are a number of questions which come to mind. For them the answers are not always the same and depend on which MA is questioned. Apart from the bio-analysis of samples from animals in non-clinical safety studies (the so-called toxico-kinetics), no other type of bio-analytical activity is cited in the GLP regulations as requiring GLP compliance. However, during inspections by MAs other types of activity are regularly inspected. If situations arise where the GLP principles are not followed, then these are criticised. Such examples have been seen during inspections by MAs of method validation. It is clear that some MAs are convinced that method validation performed on methods which are used in GLP studies should also be performed in compliance with GLP, whereas other MAs clearly state that this is not mandatory. Another example can be seen with bio-analysis performed on samples coming from clinical studies (clinical bio-analysis).

Method validation

The GLP principles require naturally that the methods used be validated. However, there are a number of situations where differences in the expectations of MAs have been noticed. Method validation is performed in laboratories prior to the use of the method in a study. However, in many sites, when the validation has been performed and the results verified by the manager, a statement indicating that the method is fit for use is prepared and signed and the method is then used in studies. A certain MA is now however requiring that full validation reports are prepared and signed prior to the use of the method in a GLP study, even though there appears to be no mention of such reports in the GLPs. During GLP inspections other MAs are making major observations not on whether or not the method was validated, nor on its GLP compliance, but of the scientific acceptability of the validation process.

Clinical bio-analysis

Such activities are becoming more and more frequently inspected by MAs, although the only relationship with the GLP principles is with the EMEA *Note for guidance on the investigation of bioavailability and bioequivalence* [9]. This states that bioequivalence studies should be performed using "appropriate GLP principles". One MA is currently setting up an inspection programme of clinical bio-analysis using good clinical practice (GCP) inspectors, but it is not clear for the moment what quality referential these inspectors will base their inspections on for the bioanalytical part of the inspection. It is important that such differences in the definition of the perimeter of GLP principles for bio-analysis be clarified and differences between national authorities be prevented. During many GLP inspections of such data much of the inspection is based not on the GLP compliance aspects of the work, but on the scientific integrity of the results and studies. Such judgements are often based against criteria which are not included in the GLP legislations, nor other legislations, but are founded on white papers or guidelines emanating from working groups of conferences, as in the case of the QC sample positioning in analytical runs and acceptance criteria as discussed previously in this paper. It is not only expected that such criteria should be followed for studies performed after such guidelines were documented, but also that studies performed prior to this date are also criticised for not complying to the expectations which were published years after the study had been completed and reported. It is necessary to ensure that the quality referential concerning such types of activity be clearly defined and that the criteria of judgement harmonised as much as possible between countries. There may certainly be a need for such inspections, but should the inspections of the scientific content of such activities be considered as a GLP inspection or should they be considered as another type of inspection?

Differences and similarities between GLP and other legislations

The laboratories which perform non-clinical safety testing and which are subjected to GLP inspections are also subjected to other legislations and to other inspections. Such legislations include those of health and safety and environment and animal welfare. In order to ensure a certain consistency among authorities in the same country, some GLP MAs are starting to perform joint inspections with other inspectorates. This is an excellent initiative, but there are still some situations which require to be resolved. Such an example concerns the requirement by a national animal welfare inspectorate which states that during non-clinical safety studies on dogs, the animals must be allowed to go out into open air compounds daily. Under such conditions, the GLP requirement to indicate in the study plan the environmental conditions under which the test system should be maintained and that the study plan should be followed becomes difficult to reconcile with the animal welfare requirements.

Activities subject to GLP legislation

What is globally required to be GLP and what is requested locally? Although there is a general consensus concerning the toxicology studies and the associated toxicokinetic phases of such studies, there still remain some areas where clarification is required. In the early 1990's the Committee Proprietary Medicinal Products (CPMP) published a list of activities subject to the European GLP legislation [8]. As well as in the case of toxicology and toxicokinetics, the list indicates in the ninth bullet point some safety pharmacology studies. The requirement to perform core dossier safety pharmacological studies according to the GLP principles

was also identified by the International Conference on Harmonization (ICH) in the harmonised tripartite Guideline S7A safet Pharmacology Studies for Human Pharmaceuticals [10]. However, there are still some discussions concerning exactly which types of study should be included in the dossier. This is due to the fact that some leeway is given so that important non-core dossier studies can also be considered as being required to be GLP compliant. The tenth bullet point of this document concerns those safety studies which are used during the release of batches of compounds produced by biological or biotechnological methods. These are commonly referred to as type 10 studies. Since the list of the ten types of studies comes from a European document, it raises the question as to the requirement to perform such type 10 studies according to the GLP principles in other global regions. Even in Europe there is no common agreement on such activities being required to be GLP compliant and particularly as to which of the various types of compound release studies on biological compounds should be GLP or GMP.

CONCLUSIONS

In this paper an attempt has been made to show that, although a lot of effort has been put into the harmonisation of the texts and the expectations of the inspectors, there is still some work to be done. The object of this article was not to criticise the MAs, but to indicate those areas where challenges still exist. The greater the harmonisation of the expectations, the easier it will be for the industry to establish global quality systems giving a better possibility for higher quality work. It is also hoped to have stimulated thoughts on the activities of the GLP staff and on their role. Should QA be checking for good science, good quality or only compliance? Should they simply be preventing fraud, improving quality or even improving science? The role of the quality professionals is changing, whether they be in the MAs or in the industry and everyone must adapt to ensure that the results are of the highest quality and that patients receive the best possible services.

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